Blue Pharmacy:
Marine Organisms in Discovery & Development of New Pharmaceuticals

Deniz Tasdemir

Research Unit Marine Natural Product Chemistry
GEOMAR Centre for Marine Biotechnology (GEOMAR-Biotech)
GEOMAR Helmholtz Centre for Ocean Research Kiel, GERMANY

GEOMAR-Biotech
GEOMAR Centre for Marine Biotechnology

GEOMAR

Better Off Blue, 27-28 September 2017, Berlin

Helmholtz Association (18 centers, 7 Institutes)

Germany's largest scientific organisation
>37K employees (>15K scientists), Budget 4 Billion € p.a.

GEOMAR Helmholtz Centre for Ocean Research Kiel

- A world-leading institute in the field of marine science
- 950 scientific and technical staff
- Annual budget of 72 Mio €

Research Divisions

- Ocean Circulation & Climate Dynamics
- Marine Biogeochemistry
- **Marine Ecology (4 RUs, RU MN - GEOMAR-Biotech)**
- Dynamics of the Ocean Floor

University of Kiel

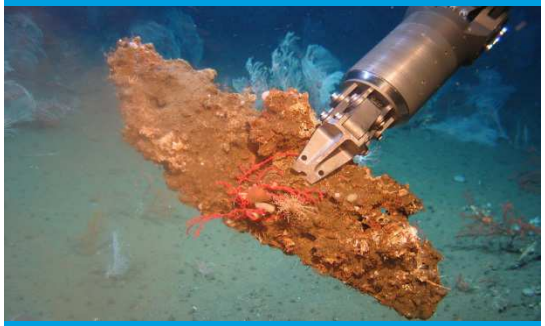
Christian-Albrechts-Universität zu Kiel

- Excellence Clusters Future Ocean, Kiel Life Sciences
- Joint teaching (Bachelor & MSc, Graduate School)

GEOMAR research vessels & large equipment

Kiel ROV (remote operating vehicle) 6000

Sample collection by Kiel ROV



AUV (automatic underwater vehicle)

MS Merian

MS Alkor

MS Polarstern

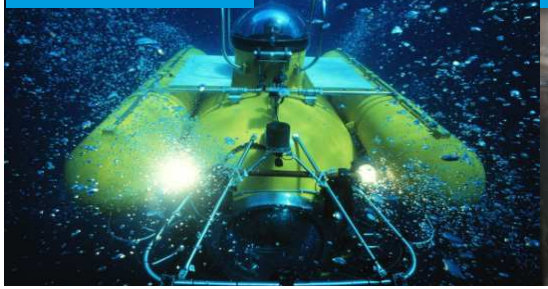
MS Meteor

MS Sonne

MS Polarfuchs

MS Littorina

Submersible Jago



KIMOCC – Organism culture facilities

Mesocosms

Kiel Benthocosm

Infrastructure –
RU Marine Natural Products Chemistry / GEOMAR-Biotech

Fermentation OSMAC, Co-culture	Automated Extraction ASE, SFE	Bioassays Ecological Pharmacological	Metabolomics DESI - MS Imaging	Fractionation Purification	Structure elucidation

Integrated Approaches for (Ecology-Driven) and Drug Discovery

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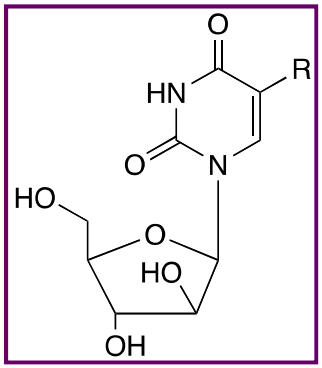
GEOMAR-Biotech
GEOMAR Centre for Marine Biotechnology

HELMHOLTZ ASSOCIATION

Overview of History & Global Marine Natural Product (MNP) Pipeline



R= H Spongouridine
R= Me Spongothymidine

Cryptotethia crypta
Bergmann & Finney
1950-1956

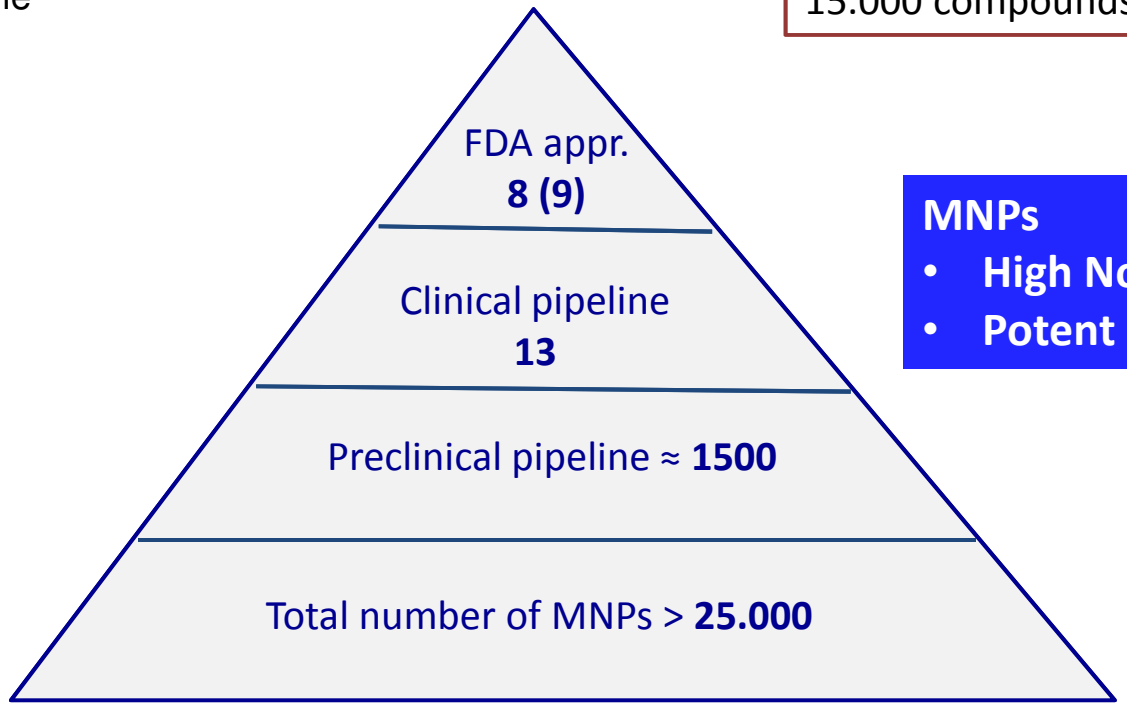
Cytarabine - 1969

1950s 1970s 1980s 1990s 2000s 2016

>25.000 MNPs
8(9) approved

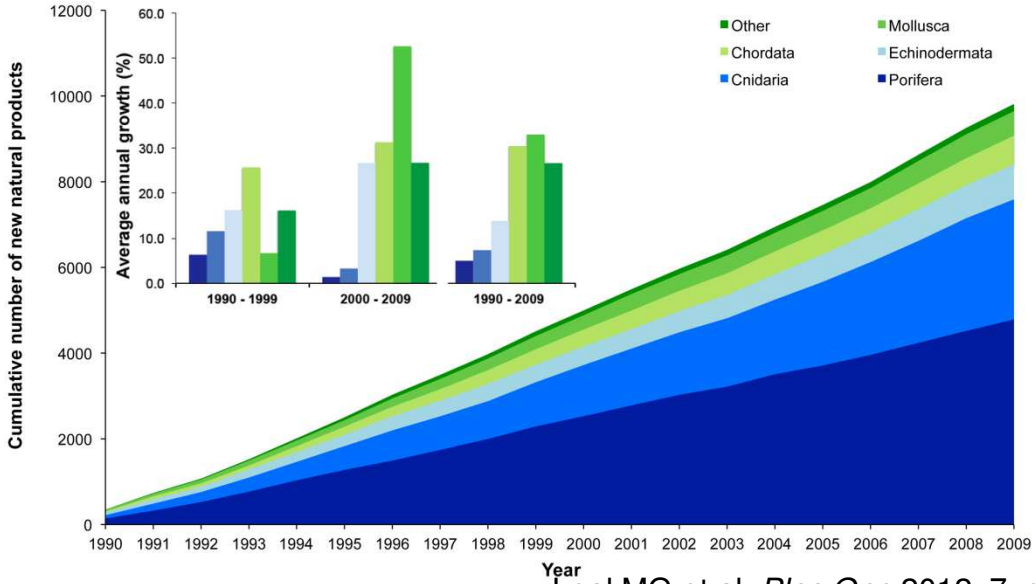
Drug Discovery

15.000 compounds: 1 Drug to clinic

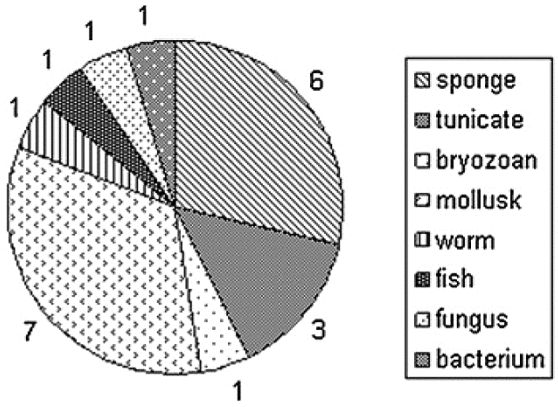


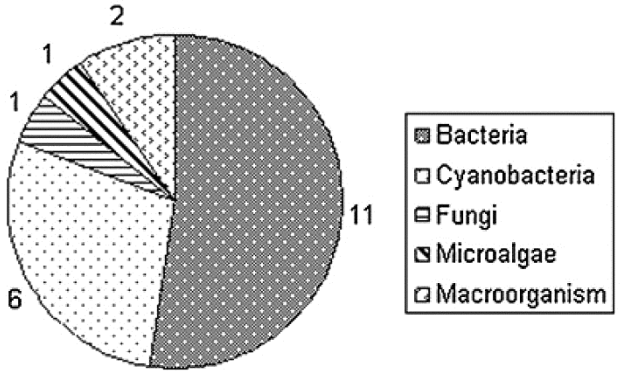
MNPs
- **High Novelty**
- **Potent Bioactivity**

Sources and Distribution



Leal MG et al. *Plos One* 2012, 7, e30580.





Origin of the MNPs

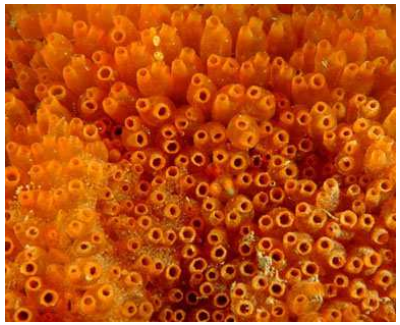
- Tropical / subtropical
- Temperate waters
- 2% from deep sea organisms
- Mainly Sponges, Cnidarians

Distribution of MNPs in clinic /clinical trials &
Their demonstrated /predicted metabolic sources

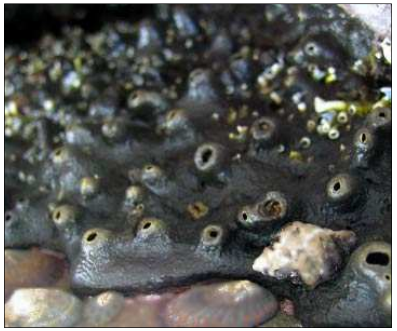
Gerwick & Fenner, *Microb. Ecol.* 2013, 65, 800-806

16 of 20 marine anticancer
drug candidates are of microbial origin

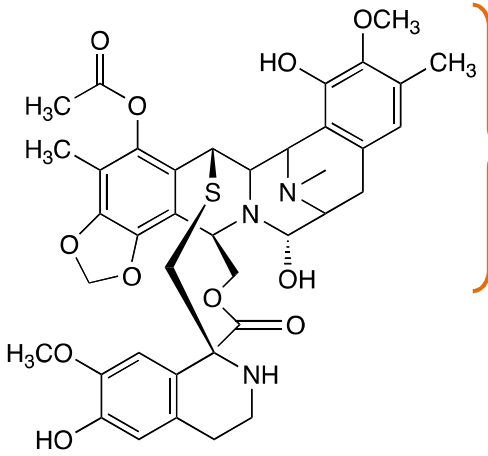
Microbial origin of MNPs



Ecteinascidea turbinata
Endoecteinascidia frumentensis



Halichondria okadai (1986)
Lissodendoryx, Phakellia, Axinella sp.



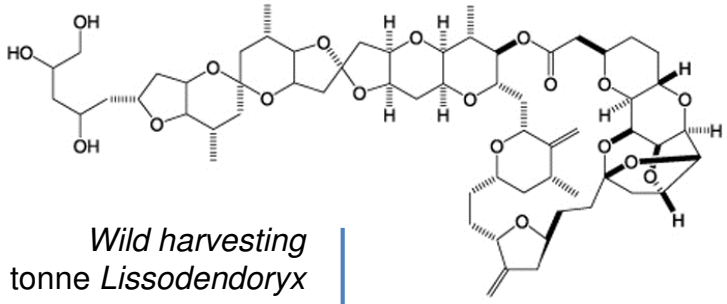
Pseudomonas fluorescens

Cyanosafracin B

21 steps

1970: Anticancer act. of extract
1990: Purification of ET-743
2007: Approval
Use: Solid cancers

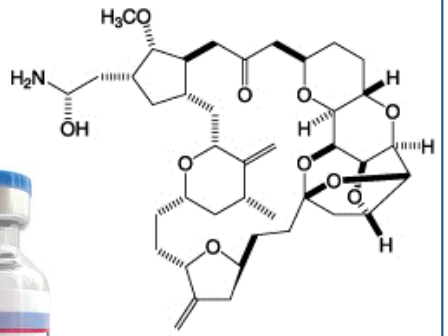
ET-743, Yondelis®



Wild harvesting
1 tonne *Lissodendoryx*

Aquaculture (NCI)
310 mg

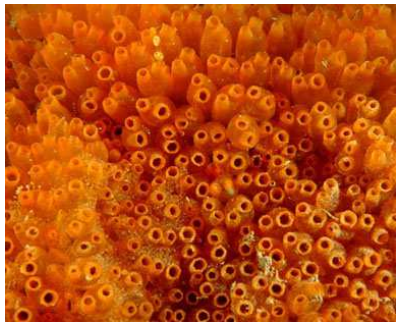
Total synthesis
truncated molecule (67 steps)



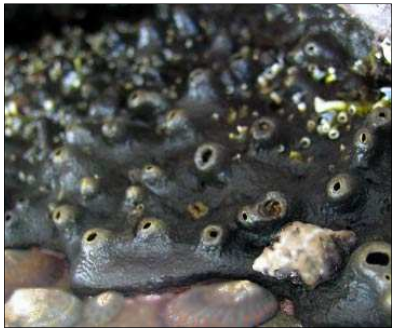
Isolation HCB: 1986
Approval: 2010 FDA
Use: Rec. breast cancer

Erubilin mesylate, Halaven®

Microbial origin of MNPs



Ecteinascidea turbinata
Endoecteinascidia frumentensis



Halichondria okadai (1986)
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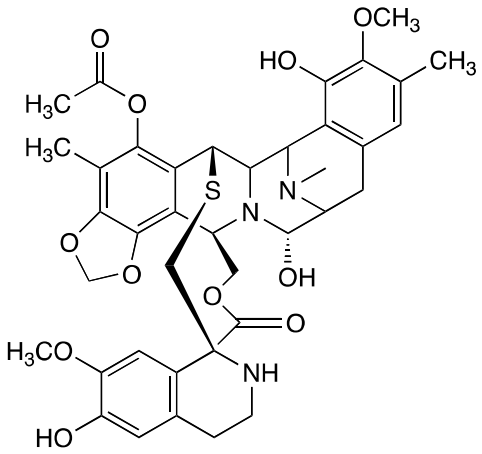
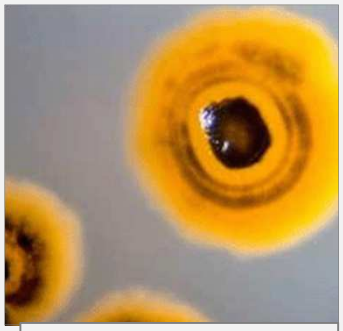
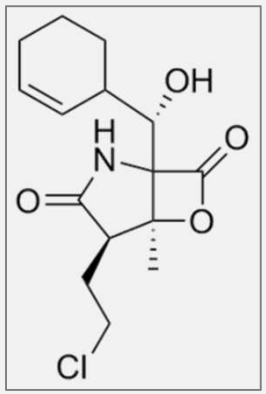
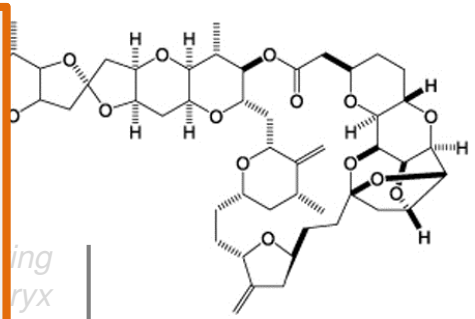


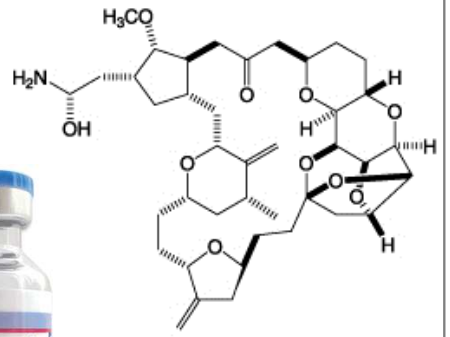


Salinospora tropica



Salinosporamide A, Anticancer





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Use: Solid cancers

ET-743, Yondelis®

Isolation HCB: 1986
Approval: 2010 FDA
Use: Rec. breast cancer

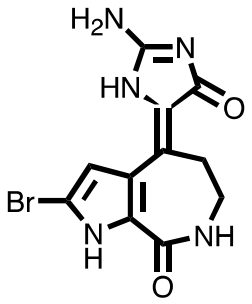
Erubilin mesylate, Halaven®

Anticancer MNPs from Marine Sponges

Stylissa massa

Xestospongia sp.

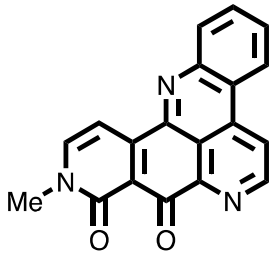
Rhabdastrella globostellata



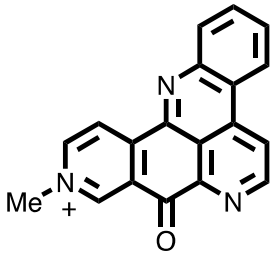
10Z-Hymenialdisine

Kinase inhibitor (MEK)
IC_{50} value 6nM

J. Med. Chem., 2002, 45, 529-532



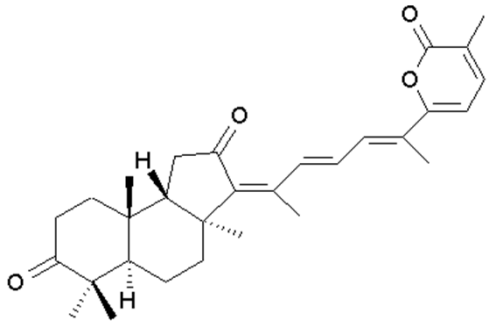
Neoamphimedine



Deoxyamphimedine

Topoisomerase II inhibitor
Equal *in vivo* activity to Etoposide

J. Org. Chem., 2001, 66, 3246-3248
Biochem. Pharm., 2003, 66, 447-458
Marine Drugs, 2009, 7, 196-209

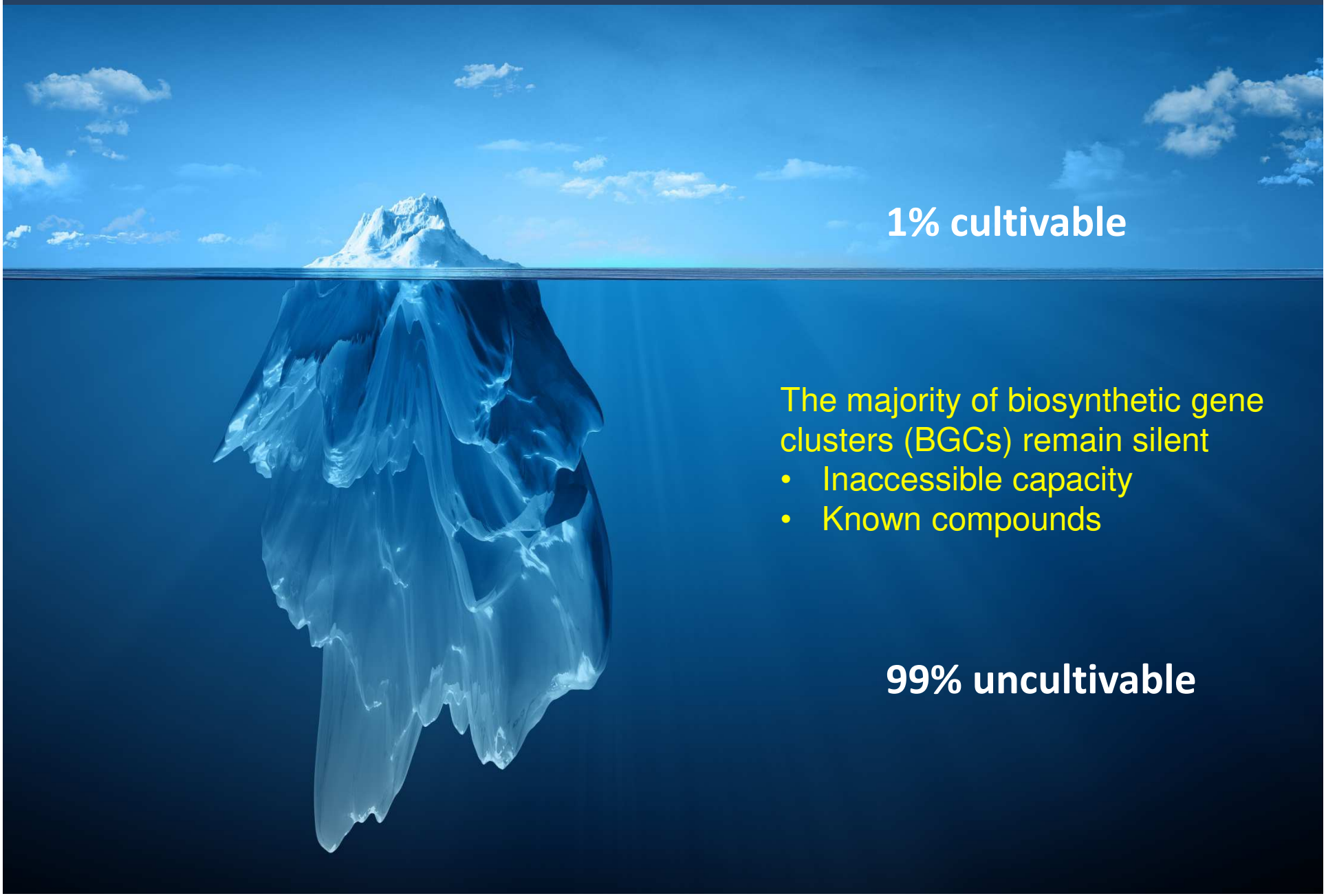


Stellettin B

Extremely potent anticancer
$p^{21WAF1/Cip1}$(-)HCT- 116
IC_{50} value 43 nM

J. Nat. Prod., 2002, 65, 210-14

Ocean's dark matter – Microbiome

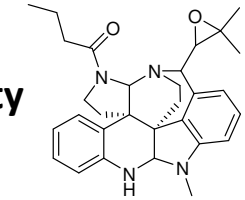


Increasing Chemodiversity - Activating Silent BGCs by OSMAC and Co-cultivation Approaches

Fungal strain

Standard: 1 type of cultivation

Limited chemical diversity



Culture regime solid/liquid

Shaking/ non-shaking

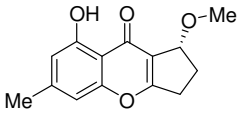
OSMAC

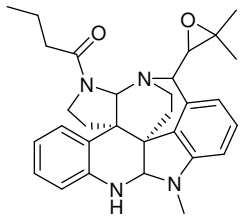
Nitrogen / carbon sources

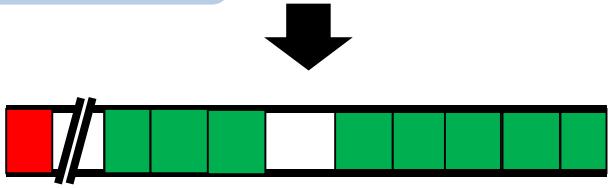
Salt

OSMAC: Activation of silent gene clusters by variation of culture conditions

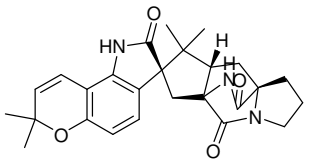
Co-cultivation: Activation of silent gene clusters by inducing chemical cross-talks, competition

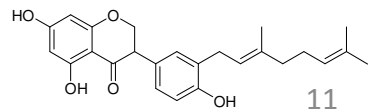




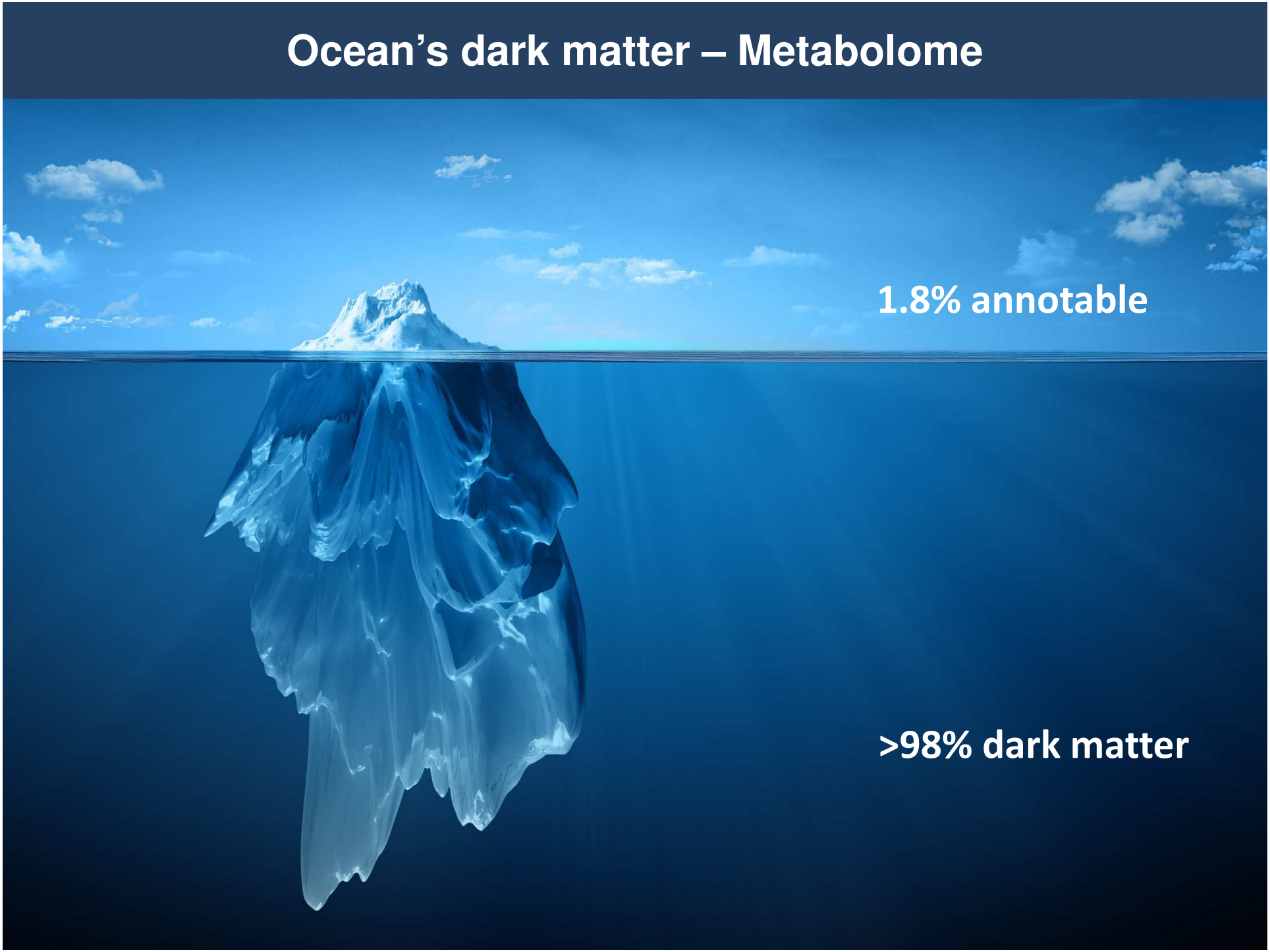


Enhanced chemical diversity





Ocean's dark matter – Metabolome



Identifying Chemical Inventory by Molecular Networking

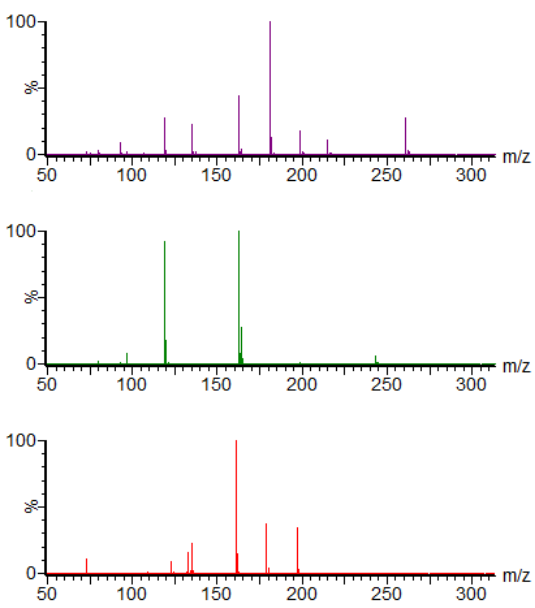
Extracts

GNPS

https://gnps.ucsd.edu

Wang et al. 2016

LC-MS/MS analysis



Tandem Mass Spectrometry Data

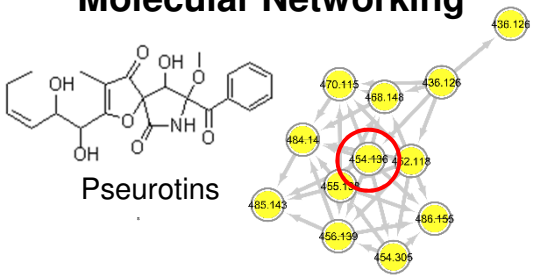
GNPS

MS/MS spectra comparison

- Annotation of putative known compounds (using MS/MS databases)

➔ Dereplication

Molecular Networking



Pseurotins

Clustering data based on MS/MS spectra similarities

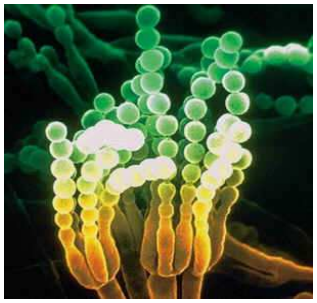
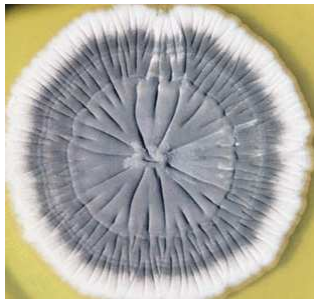
➔ Global chemical diversity overview

➔ Known / unknown molecular clusters

Why Fungi, Why Marine Fungi / Marine Fungal Natural Products?






2014. Marine Fungal Natural Products (MaFNaP) Consortium

- To intensify the systematic research on **marine fungal natural products**
- To stimulate networking and collaborations for joint research
- **Unlock the real capacity of marine fungi for products & processes!**

2015. Inaugural MaFNaP conference, Nantes (France)

Why Fungi, Why Marine Fungi / Marine Fungal Natural Products?

2nd International Conference of Marine Fungal Natural Products (MaFNaP_2017)

27-29 June 2017
Kiel, Germany

3rd MaFNaP_2019: 26 – 28 June 2019, Athens, Greece

Baltic Blue Biotechnology ALLIANCE

Advancing marine biobased product development

Lead partner: GEOMAR

Duration: 3 years (March 2016)

Budget: € 3.4 M

Management: SUBMARINER Network EEIG

www.balticbluebioalliance.eu

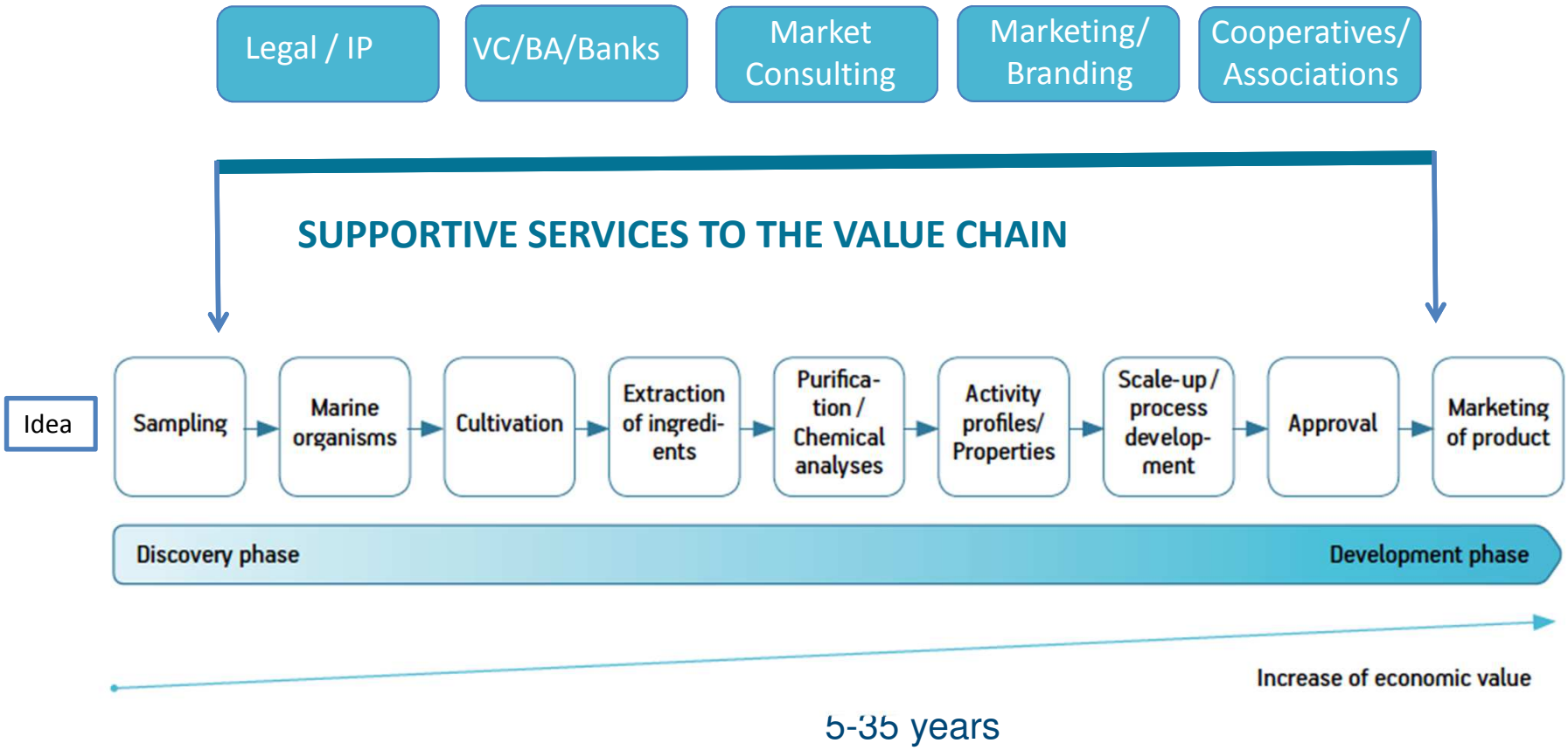
#BalticBlueBioAlliance

BalticBlueBio ALLIANCE Consortium: Research organizations, biotech hubs, business parks, SUBMARINER Network, companies..

Expertise: Aquaculture, chemistry, microbiology, waste water treatments, life cycle analysis, aquatic ecology, IP-TT, marketing..

Partner		Function	Partner		Function
GEOMAR	DE	**Lead, WP2**	CRM	DE	**Case owner**
SUBMARINER Network EEIG	DE	**P, WP4**	Biovento Sp. z.o.o	PL	**Case owner**
BioCon Valley GmbH	DE	P	JSC 'Geoterma'	LT	**Case owner**
KTH Royal Institute of Technology	SE	P	JSC 'Baltic Probiotics'	LV	**Case owner**
University of Gothenburg	SE	P	Kalundborg Utility A/S	DK	**Case owner**
Finnish Environment Institute (SYKE)	FI	P			
University of Gdansk	PL	P	**6 new funded partners**	---	
Pomeranian Special Economic Zone Lt	PL	P			
Coastal Research & Planning Institute	LT	P	**9 cases for mentorship**		
Danish Techn. Institute (DTI)	DK	**P, WP3**			
Klaipeda Sci & Techn Park (KSTP)	LT	P			
Latvian Biotech. Assoc. (LBA)	LV	P	Agro Business Park	DK	Associated Partner
Tartu Biotechnology Park SA	EE	P	ESMB	FR	Associated Partner
Svanvid Sp. z.o.o	PL	P	CIIMAR	PT	Associated Partner
SAMS	UK	P	University of Greifswald	DE	Associated Partner

Blue Biotechnology pipeline / full value chain



GEOMAR

SUBMARINER NETWORK

Interreg Baltic Sea Region

ALLIANCE

Background: Submariner Compendium, Roadmap; Sustainable BG agenda for BSR EC 2014

The challenge: No integrated blue biotech value chains in the BSR!

Resources and expertise are present but too **fragmented** to make full use of innovation & market uptake potential

No single actor can cover the **full range of services** across the whole value chain

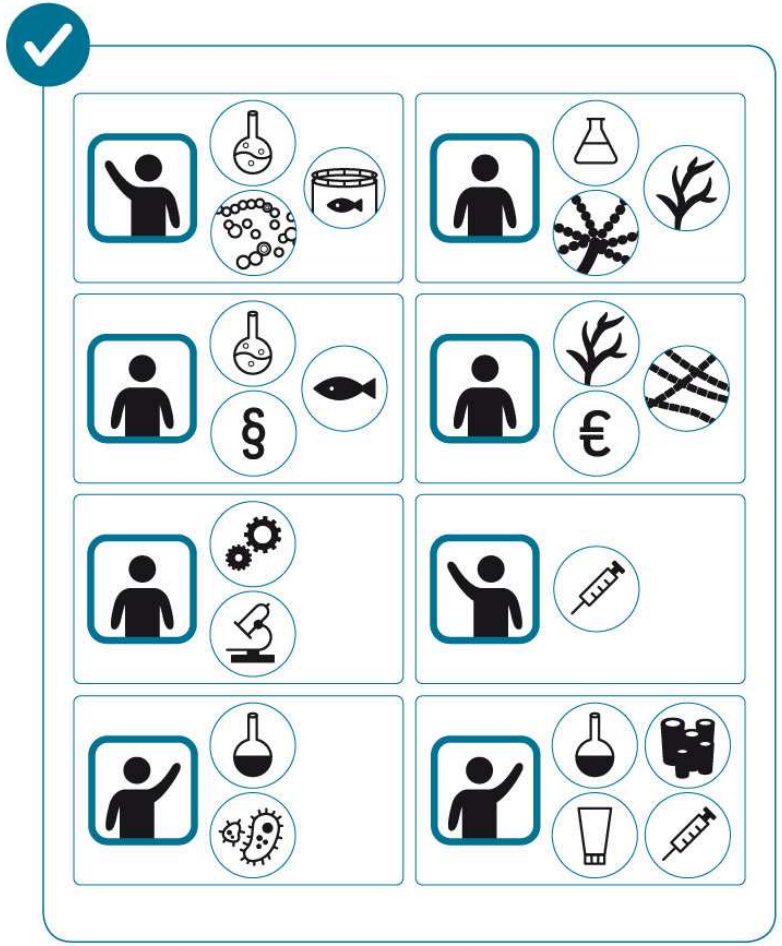
Need for reaching the **critical mass** through **systematic cooperation** to pool national resources and expertise

The sector needs **concrete success stories** in product development to showcase the economic potential

Accelerating the development of marine bio-based products through translational collaboration of Public& private partners

GEOMAR SUBMARINER NETWORK Interreg Baltic Sea Region ALLIANCE

What / How we want to achieve



Work with **real "client" cases** as the starting point

Understand **case owners' needs** to advance in product development

A needs-oriented **service offer**, e.g.

- Mentoring (2-3 mentors-site visits)
- Map infrastructure & service offers
- Partner search and match-making
- Marketing, legal, financial advise

Match cases to the right **services, facilities and experts** throughout the BSR

Offer expertise, labs, facilities, resources to case partners

Proactive search for new actors (cases)

- calls, pitching events, joint marketing

A **self-sustaining network** of actors providing service offers

Interreg Baltic Sea Region
ALLIANCE

GEOMAR

SUBMARINER NETWORK

The first generation cases

Case 1. Baltic macroalgae in global cosmetics

New product based on macroalgal extracts

Application in cosmetics to protect skin from free radicals

Alliance helping to find extraction method/upscaling

CRM
Coastal Research & Management

Levent Piker
CRM, Kiel | Germany

Case 2. Search for antifouling compounds for ship industry

Start-up hopes to identify algae growth inhibitors in its microalgae collection

Alliance helping with bioactivity testing, extraction methods, chemistry and market research

Biovento

Natalia Kujawska
Biovento | Poland

Case 3. Microalgae facility for hire

Putting an existing state-of-the-art microalgae test facility to new use as a test and research facility

Alliance helping to develop concept and identify new users

KALUNDBORG FORSYNING

Preben Thisgaard
Kalundborg Utility | Denmark

Case 4. Healthy fish, happy customers

Company working on probiotics-based products applications in fish aquaculture

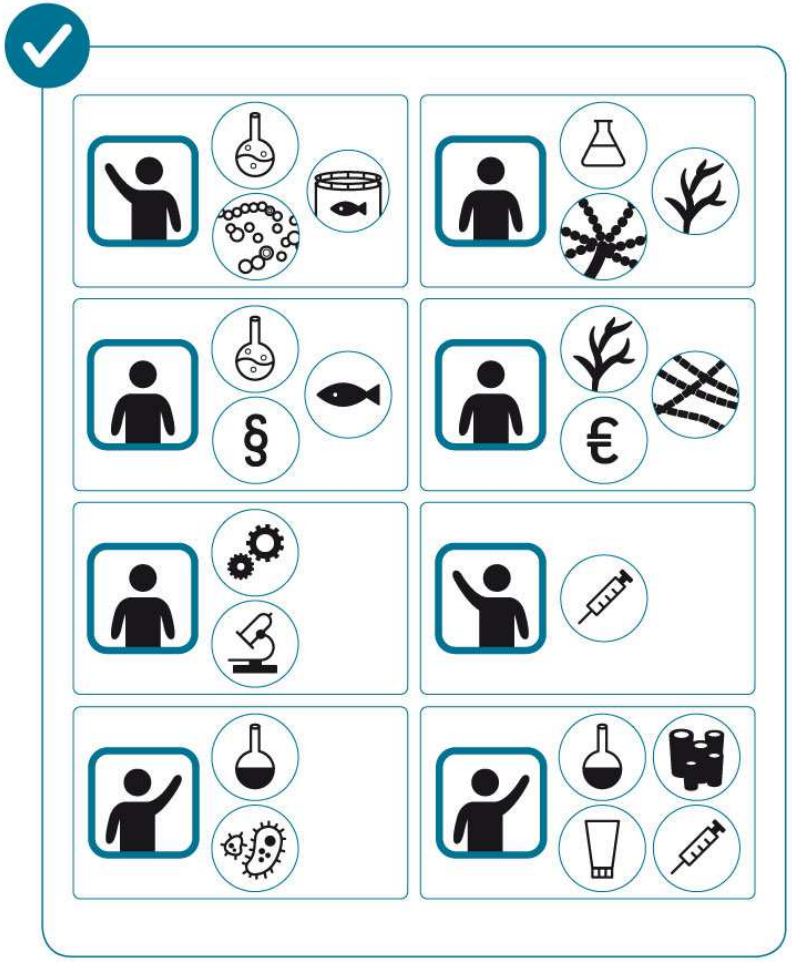
Promote fish health & reduce the need for antibiotics in aquaculture

Alliance helps with extraction, market research and product development

bp baltic probiotics

Arta Bārdule
Baltic Probiotics | Latvia

Expected outcomes



- BSR-wide partnership of academia & industry to facilitate blue biotech
- Develop/advance innovative marine bio-based **products and services**
- Develop optimal transnational pathways
- Single information & cooperation hub (database) - GEOMAR
- Reach the critical mass
- Increase global competitiveness of BSR-foster transition to eco-friendly production

Set example for European Blue Biotech?

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Interreg Baltic Sea Region

ALLIANCE

BalticBlueBioAlliance pitching & match-making event

8-10 November, Berlin

www.balticbluebioalliance.eu

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SUB-MARINER NETWORK

Interreg Baltic Sea Region

ALLIANCE